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Controversy

Reconsider radiation exposure from imaging during immune checkpoint inhibitor trials to reduce risk of secondary cancers in long-term survivors?

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ABSTRACT

Immune checkpoint inhibitors (ICI) have improved outcomes for patients with advanced cancers, and results in increasing numbers of long-term survivors. For registration studies, progression-free survival and disease-free survival often serve as primary endpoints. This requires repeated computed tomography (CT) scans for tumour imaging which might lead to major radiation exposure. To determine this, all immune checkpoint inhibitors trials that led to FDA approval were retrieved up to July 29, 2019. From the available protocols, imaging modalities and schedules used in each trial were identified. The anticipated cumulative number of scans made after 1, 3, 5, and 10 years study participation were calculated. The percentage of lifetime attributable cancer risk was calculated using the Biological Effects of Ionizing Radiation VII report. Fifty-one trials were identified, from which 39 protocols were retrieved. Four were adjuvant trials. All protocols required repeated chest-abdomen imaging and specified CT scans as preferred imaging modality. Median calculated cumulative numbers of chest-abdomen CT scans after 1, 3, 5, and 10 years study participation were 7, 16, 24 and 46, respectively. For ages 20–70 years at study entry, the average lifetime attributable cancer risk after 1 year of study participation ranged from 1.11 to 0.40% for men and from 1.87 to 0.46% for women. At 10 years study participation, this risk increased to a range of 5.91 to 1.96% for men and 9.64 to 2.32% for women. Given high imaging radiation exposure for long-term survivors in current ICI trials an adaptive imaging interval and imaging termination rules should be considered for long-term survivors.

Introduction

Immune checkpoint inhibitors (ICI) have improved the outcomes for patients with advanced cancers, also resulting in increased numbers of long-term survivors in subgroups of patients with metastatic disease or irresectable tumors. In advanced stage melanoma, for example, a pooled analysis has shown an overall survival (OS) rate of 20% at 10 years in patients treated with ipilimumab. An OS rate of 34% at 5 years was seen when given a programmed cell death protein 1 (PD-1) antibody, for treatment-naïve patients this was 40% [1–3]. Increased numbers of long-term survivors in a subgroup were also observed in other diseases, including a 5-year OS rate of 28% in heavily pre-treated patients with renal cell cancer and a 16% OS rate with non-small-cell lung carcinoma [4]. Moreover, ICI has increased long-term OS in the adjuvant setting in patients with melanoma [5].

For registration studies, progression-free survival (PFS) and disease-free survival (DFS) often serve as primary endpoints. This requires repeated computed tomography (CT) scans for tumor imaging. Given the expanding group of patients experiencing long-term survival from ICI, trial participation could therefore lead to major radiation exposure. This ionizing radiation can induce DNA damage and increases the risk of second cancer development [6].

The aim of this study was to analyze protocols of ICI trials to determine expected imaging radiation exposure. Information regarding radiation exposure during screening, treatment and follow-up was extracted and used to estimate the lifetime attributable risk (LAR) of radiation-induced cancer.

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Methods

Trial and protocol identification

All ICI trials that led to Food and Drug Administration (FDA) approval were identified up to July 29, 2019. Protocols were collected from the journals in which trial results were published as well as from ClinicalTrials.gov.

Imaging data acquisition

The imaging modalities that were allowed in the protocols were identified and the corresponding radiation exposure for trial participants was calculated for 1, 3, 5 and 10 years of study participation. The protocols were checked for specification of an adaptive imaging interval for long-term survivors that extended the imaging interval to > 3 months. We also reviewed whether the protocols specified imaging termination criteria for long-term survivors and a risk/benefit assessment for exposure to ionizing radiation from imaging.

Calculation of the imaging-induced lifetime attributable cancer risk

We calculated the LAR of imaging-radiation-induced cancer by using the risk estimates published in the Biological Effects of Ionizing Radiation (BEIR) VII report [7], which estimated the LAR of cancer resulting from a single 0.1 Gy dose based on sex, age and exposed organs. We interpolated the age of exposure to the nearest year of age. For our calculations, a dose of 16.5 mSv was used for a chest-abdomen CT scan (in oncology this includes the pelvis). This was the mean effective radiation dose of a chest-abdomen CT scan reported in a recent analysis of standardized data from over 2 million CT scans in adults obtained at institutions in Europe, the U.S.A., Israel and Japan [8].

Results

Trial and protocols

The search yielded 51 trials, four of which were in the adjuvant setting and the others in the metastatic setting. For 12 trials the protocols were not publicly available and were excluded, 39 trials were analyzed. All included trials were of recent date (2011–2019).

Imaging modalities and protocols

All protocols included mandatory repeated imaging of the chest and abdomen. Although 33 protocols specified MRI as an alternative, 19 of them stated that CT scans were preferred or that MRI scans were allowed only if CT scans were contraindicated. Another five protocols stated that MRI scans were allowed for abdomen but not for chest imaging. If imaging of the brain was requested, MRI was preferred. Therefore, brain imaging rarely contributed to radiation exposure. Other less common imaging modalities are summarized in Supplementary Appendix Table 1 with data retrieved for these modalities and the imaging protocols used.

Eight trials, three in the adjuvant setting, had an adaptive increasing imaging interval with longer follow up. Four trials, including one adjuvant trial, had criteria for imaging termination. Only the adjuvant CheckMate 238 trial had both and therefore requested the fewest scans.

All 39 trials required that the same assessment method and the same technique be used during the trial and follow-up. Only the adjuvant CheckMate 238 trial, provided an imaging-induced ionizing radiation risk/benefit assessment.

Fig. 1 shows the estimated number of protocol-requested chest-abdomen scans made after 1, 3, 5 and 10 years of study participation in the ICI trials. The median cumulative number of chest-abdomen CT scans per patient after each of these four time points were 7, 16, 24 and 46. In the four adjuvant trials, the total number of such scans per patient ranged between 5–7, 11–16, 15–24 and 15–46, respectively.

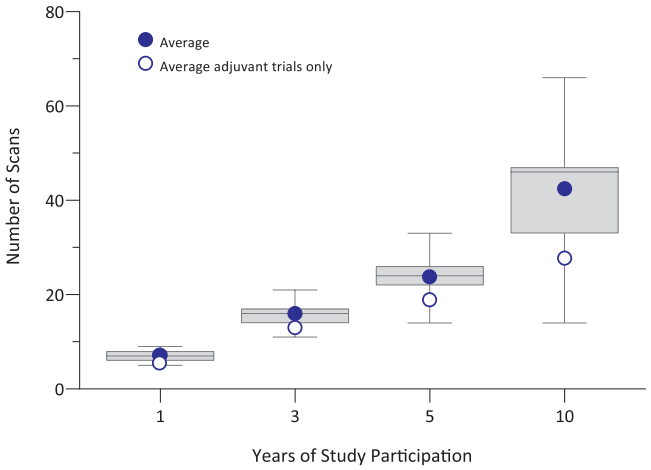

Fig. 1. Estimated number of protocol-requested chest-abdomen scans (CT or MRI) in the immune checkpoint inhibitor trials. Data from 39 trials, of which four were adjuvant trials. The box-and-whisker plot represents the estimated number of scans after 1, 3, 5 and 10 years study participation in immune checkpoint inhibitor trials. The boxes represent the median cumulative number of chest-abdomen CT scans per patient after each of these four time points: 7, 16, 24 and 46 (horizontal bar) and quartile one and three (lower and upper ends of boxes). The whiskers extend to the highest (9, 21, 33, 66) and lowest (5, 11, 14 and 14) numbers of scans for each time point.

Calculation of LAR of radiation-induced cancer

The LAR of secondary cancer depends on the cumulative radiation dose, which increases with longer trial participation. Furthermore, it depends on the patient's age at the start of study participation and on the patient's sex. After 1 year of trial participation, the average LAR was 1.11% for a 20-year-old male and 1.87% for a 20-year-old female. With higher age at start of study participation, the average LAR was lower. For example, the average LAR was 0.40% for 70-year-old males and 0.46% for 70-year-old females. After 10 years of study participation the LAR increased to 5.91–1.96% for men and 9.64–2.32% for women (for ages between 20 and 70 at study entry). Figs. 2 and 3 show the estimated LAR of cancer for patients in ICI trials with different ages at the start of study participation.

Discussion

This study shows that ICI trials for FDA registration used imaging protocols that resulted in high cumulative radiation exposure for patients. This exposure can induce secondary cancers in long-term survivors, with the highest risk in young women.

The risk of carcinogenesis due to ionizing radiation from CT scanning in patients with solid tumors has become increasingly apparent [6], especially after patients with metastasized testicular cancer achieved complete remissions and cures. Consequently, it became obvious that imaging procedures had to be reduced to avoid secondary cancer [9,10]. Before the ICI era, patients with advanced solid cancer apart from testicular cancer patients, had a very high chance of recurrence or progressive disease and did not live long enough to develop imaging induced secondary cancer. However, ICI improved the outcomes for a subgroup of patients with advanced solid cancers, resulting in increased number of long-term survivors, some of them may even be cured [1–3]. As shown in our analysis, these long-term survivors have a high risk to develop secondary cancer due to imaging radiation. Although regular response measurements of patients in ICI trials is of importance to avoid continuation of an inactive treatment and to

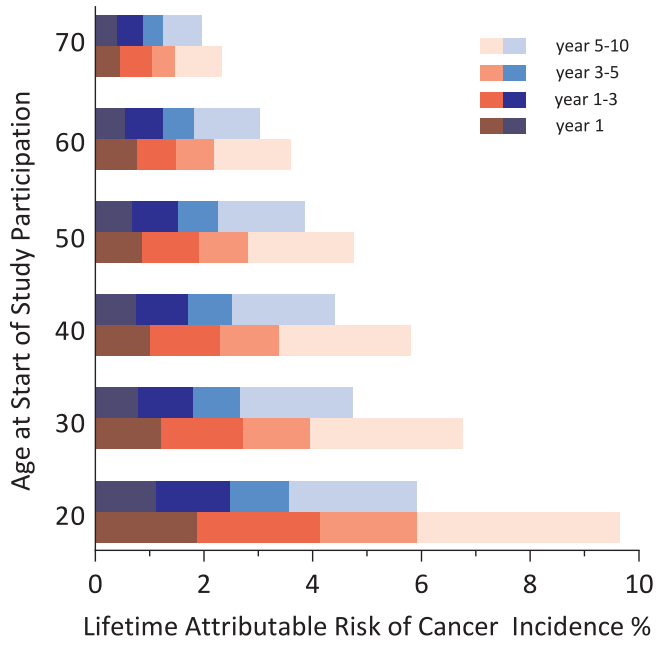

Fig. 2. Average lifetime attributable risk (LAR) of imaging-radiation-induced cancer incidence. The stacked bar chart represents the estimated average LAR of cancer due to protocol-requested chest-abdomen CT scans in all immune checkpoint inhibitor trials analyzed: 39 trials of which 4 were adjuvant trials. The analysis was based on an estimated effective dose 16.5 mSv. The data are presented separately for males (blue) and females (red).

determine PFS or DFS, we now have to consider the radiation burden as well. This requires that we have to balance the pros and cons of frequent imaging in long-term survivors in ICI trials.

Our results show that a similar approach as for testicular cancer patients should be considered regarding imaging procedures during and after ICI treatment. Investigators can use the ICRP publication 62 for assessing if the use of radiation is justified [11]. It adheres to the as low as reasonably achievable (ALARA) principle of radiation safety designed to minimize radiation doses and release of radioactive materials. To justify radiation, the risk / benefit ratio should be described.

The cumulative imaging radiation dose can be reduced by optimizing CT protocols. Currently, the CT scan radiation dose varies greatly between countries and institutions. For example, the mean effective dose of a chest-abdomen CT scan in Germany is 10.0 mSv, while this is 37.9 mSv in Japan [8]. This variation is attributable to scan parameter settings and reconstruction algorithms and not to patient characteristics or the machine manufacturer or model [8]. Protocol sharing across institutions could help optimize and standardize CT effective doses [8]. Moreover, an adapted imaging interval, meaning longer imaging intervals with longer follow up, which was used in three of the four of adjuvant ICI studies we analyzed (Figs. 1 and 3), could reduce radiation burden. In future trials, CT scans could also be replaced, where possible, by other modalities such as MRI scans [12]. Improved accessibility and advanced technology have accelerated the use of MRI and its acceptance in clinical practice [11]. Furthermore, software that automates imaging radiation dose tracking in electronic patient files could give treating physicians real-time insight into the total radiation exposure of their patients [13].

Our analysis has a few limitations. First, the calculations were done by using the risk estimates of the BEIR VII report which uses the linear no-threshold (LNT) model [7]. The LNT model provides a risk estimate based on the assumption that long-term, biological damage caused by ionizing radiation is directly proportional to the radiation dose. Any exposure to ionizing radiation, however small, can induce cancer. The sum of several very small exposures is considered to have the same effect as one larger exposure (response linearity). The general validity of the LNT hypothesis for extrapolations from effects of high to repeated low doses has been questioned [14,15]. However, evidence is provided for the existence of nonlinear biological responses in the low and medium dose range as well as effects other than the classical DNA damage [16]. In a retrospective cohort study a positive association between radiation dose from CT scans and leukaemia (excess relative risk per mGy 0.036, 95% CI 0.005–0.120; p = 0.0097) and brain tumours (0.023, 0.010–0.049; p = 0.0001) was seen [17]. The model is also recommended by advisory bodies such as the International Commission on Radiological Protection (ICRP) [18]. Therefore, we think this model

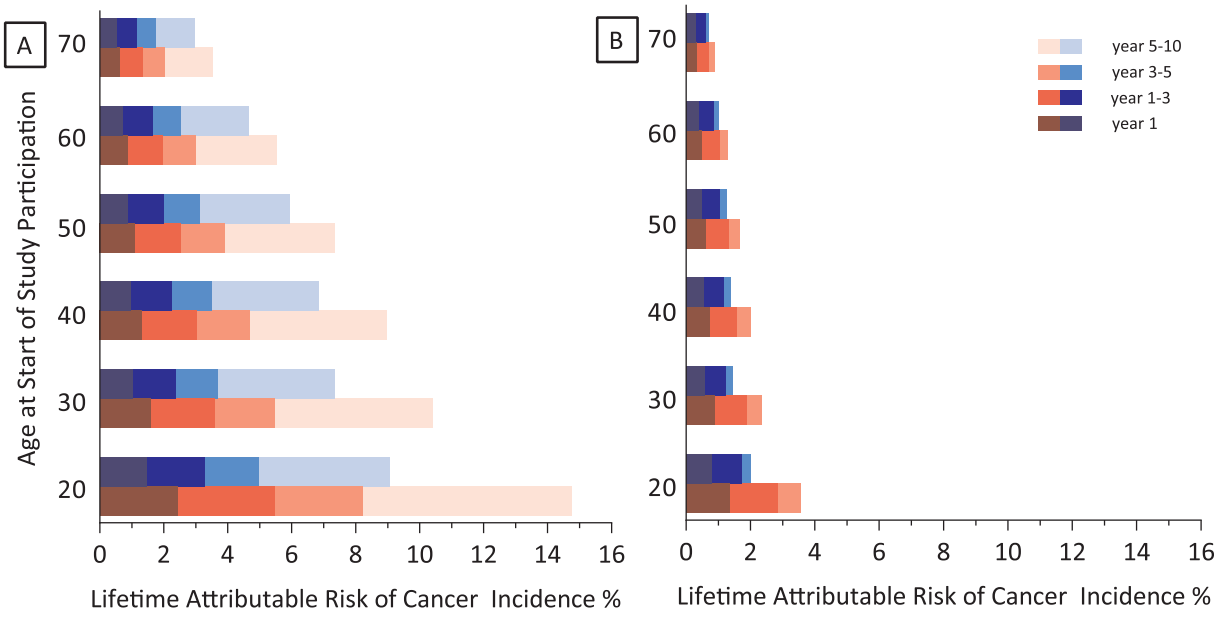

Fig. 3. Maximum and minimum lifetime attributable risk (LAR) of imaging radiation induced cancer incidence. The stacked bar chart represents the estimated lifetime attributable risk (LAR) of cancer due to protocol-requested chest-abdomen CT scans based on an estimated effective dose 16.5 mSv. A: The LAR of cancer for the trial whose imaging protocol required the highest number of scans. B: The LAR of cancer for the trial (an adjuvant trial) whose imaging protocol required the lowest number of scans. The data are presented separately for males (blue) and females (red).

is the appropriate model to use in the setting of mandatory repeated CT scans over a protracted period. Nevertheless, it should be emphasized that the LNT model can be considered a conservative approach. Therefore, the risk to develop cancer is probably lower. Secondly, for a standardized U.S. population, the BEIR VII report predicts a cancer baseline lifetime incidence of 44.9% for males and 37.5% for females due to all causes [7]. Patients that have had a primary malignancy have an increased risk for a secondary malignancy due to various reasons. Therefore, the baseline lifetime incidence of cancer is probably higher for these patients which could have influenced results. It could also be argued that some patients that already developed cancer could be more vulnerable to the mutagenic effects of diagnostic radiation due to diminished DNA repair mechanisms.

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CRediT authorship contribution statement

Daan G. Knapen: Conceptualization, Methodology, Formal analysis, Data curation, Writing - original draft. **Derk Jan A. de Groot:** Conceptualization, Methodology, Data curation, Writing - review & editing. **Thomas C. Kwee:** Formal analysis, Writing - review & editing. **Emmy I.M. Meijne:** Formal analysis, Writing - review & editing. **Rudolf S.N. Fehrmann:** Writing - review & editing. **Elisabeth G.E. de Vries:** Conceptualization, Methodology, Writing - review & editing, Supervision.

Declaration of Competing Interest

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Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctrv.2020.102027.

References

[1] Schadendorf D, Hodi FS, Robert C, et al. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J Clin Oncol 2015;33(17):1889–94.
[2] Hamid O, Robert C, Daud A, et al. Five-year survival outcomes for patients with advanced melanoma treated with pembrolizumab in KEYNOTE-001. Ann Oncol 2019;30(4):582–8.
[3] Schachter J, Ribas A, Long GV, et al. Pembrolizumab versus ipilimumab for advanced melanoma: final overall survival results of a multicentre, randomised, open-label phase 3 study (KEYNOTE-006). Lancet 2017;390(10105):1853–62.
[4] Topalian SL, Hodi FS, Brahmer JR, et al. Five-year survival and correlates among patients with advanced melanoma, renal cell carcinoma, or non–small cell lung cancer treated with nivolumab. JAMA Oncol 2019. [published online July 25, 2019].
[5] Tarhini AA, Lee SJ, Hodi FS, et al. United States Intergroup E1609: A phase III randomized study of adjuvant ipilimumab (3 or 10 mg/kg) versus high-dose interferon-α2b for resected high-risk melanoma. J Clin Oncol 2019;37. (Suppl; abstr 9504).
[6] Brenner DJ, Hall EJ. Computed tomography-an increasing source of radiation exposure. N Engl J Med 2007;357:2277–84.
[7] National Research Council of the National Academies. Health risks from exposure to low levels of ionizing radiation: BEIR VII Phase 2. Washington, DC: The National Academies Press (US); 2006. p. 245.
[8] Smith-Bindman R, Wang Y, Chu P, et al. International variation in radiation dose for computed tomography examinations: prospective cohort study. BMJ 2019;364:k4931.
[9] Honecker F, Aparicio J, Berney D, et al. ESMO Consensus Conference Guidelines on testicular germ cell cancer: diagnosis, treatment and follow-up. Ann Oncol 2018;29:1658–86.
[10] NCCN Testicular Cancer Version 1.2020. Accessed at https://www.nccn.org/professionals/physician_gls/pdf/testicular.pdf [on October 10, 2019].
[11] ICRP. Radiological protection in biomedical research. ICRP Publication 62. Ann ICRP 1992:22.
[12] Morone M, Bali MA, Tunariu N, et al. Whole-body MRI: current applications in oncology. AJR Am J Roentgenol 2017;209(6):W336–49.
[13] Talati RK, Dunkin J, Parikh S, Moore WH. Current methods of monitoring radiation exposure from CT. J Am Coll Radiol 2013;10(9):702–7.
[14] Cuttler JM. Commentary on using LNT for radiation protection and risk assessment. Dose Response 2010;8(3):378–83.
[15] Siegel JA, Greenspan BS, Maurer AH, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: A call for reassessment. J Nucl Med 2018;59(7):1017–9.
[16] Averbeck D, Salomaa S, Bouffler S, Ottolenghi A, Smyth V, Sabatier L. Progress in low dose health risk research: Novel effects and new concepts in low dose radiobiology. Mutat Res 2018;776:46–69.
[17] Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 2012;380:499–505.
[18] ICRP Publication 103. Recommendations of the international commission on radiological protection. Ann ICRP 2007;2007(37):1–332.